Journal of Stem Cell Research

Genesis-JSCR-7(2)-86
Volume 7| Issue 2
Open Access
ISSN: 2582-8797

Distraction Arthroplasty Combined with Mesenchymal Stem Cell Therapy for Ankle Osteoarthritis: A Report of Two Cases with Histological Outcomes

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Citation: Slater G, Wu C, Li JJ, Salleh R, Salleh A. Distraction Arthroplasty Combined with Mesenchymal Stem Cell Therapy for Ankle Osteoarthritis: A Report of Two Cases with Histological Outcomes. J Stem Cell Res. 7(2):1-11.

Received: May 09, 2026 | **Published**: May 24, 2026

Abstract

Distraction arthroplasty, a joint-preserving technique, combined with mesenchymal stem cell (MSC) therapy, offers a novel approach to treating ankle osteoarthritis (OA). This article presents two cases of ankle OA managed with distraction arthroplasty and intra-articular MSC injections. Arthroscopic biopsies performed at the conclusion of treatment revealed distinct cartilage repair outcomes: one case showed fibrocartilage with embedded chondrocytes, while the other demonstrated hyaline-like cartilage regeneration. These findings highlight a combined approach to promote articular cartilage repair in ankle OA, and the possible emergence of a new fibrocartilage-chondrocyte tissue type. This report discusses clinical outcomes, histological findings, and potential underlying mechanisms, providing a foundation for future research into regenerative orthopaedic therapies.

Keywords

Ankle Osteoarthritis; Distraction Arthroplasty; Mesenchymal Stem Cells; Cartilage Regeneration; Histology; Case Report.

Introduction

Ankle osteoarthritis (OA) is a progressive condition characterized by cartilage loss, subchondral bone changes, and joint dysfunction, often resulting from trauma, biomechanical abnormalities, or idiopathic

causes. Unlike knee or hip OA, ankle OA disproportionately affects younger patients, posing challenges for long-term joint preservation. Ankle OA has a prevalence of 3.4% in the general population, but can be much higher in athletes. For example, in former professional football and rugby players, the prevalence of ankle OA is 9% to 19% and 4.6% respectively [1]. Unlike hip and knee OA, the majority of ankle OA cases are post-traumatic (70%–78%) and affect younger patients [2], where single year data shows ankle OA (54%) is much higher compared to hip (8%) and knee (12.5%) OA. A high correlation of up to 70% of ankle OA cases are linked to previous ankle injuries, where ankle sprains and fractures are the most common injuries leading to OA progression [3]. Further, ankle OA patients suffer more rapid loss of function than OA in other joints, with progression to advanced disease stages within 10 to 20 years of OA onset, while clinical studies show initial degenerative changes secondary to ankle fracture developing within 12 to 18 months of traumatic injury [2,4]. Therefore, elevated prevalence of ankle OA due to injuries within athletes and younger people drives a need for better and more targeted treatment.

Although ankle OA is less common in people under 40 (22%) [5], qualitative studies [7] highlight that ankle OA patients experience pain, stiffness, swelling, balance issues, and concerns about falling, impacting their ability to participate in daily activities, work and social engagements. Moreover, younger individuals with ankle OA experience a greater reduction in physical quality of life (QoL) compared to older individuals, suggesting that early onset or progression of ankle OA may be detrimental to physical and mental well-being [1]. The early treatment of these individuals is therefore important to maintain quality of life, where physical component summary (PCS) scores note a lower median (45) compared to matched controls (52). Mental component summary (MCS) scores similarly reflect that of PCS scores, with a lower median (43) compared to controls (53) [1,6].

Traditional treatments, such as ankle arthrodesis or total ankle replacement, often compromise joint function or durability, particularly in active individuals. Distraction arthroplasty (DA), which uses external fixation to offload the joint and create a regenerative microenvironment, has emerged as a promising alternative. When DA is combined with mesenchymal stem cell (MSC) therapy, which leverages the chondrogenic and anti-inflammatory properties of MSCs, this dual approach may greatly enhance cartilage repair and delay the need for joint replacement surgery.

MSC therapy is emerging as a promising treatment option for various ankle conditions, including OA, cartilage damage, and tendon/ligament injuries [8]. In current trials, MSC therapy typically uses autologous stem cells, harvested from the patient's bone marrow or adipose tissue [9]. Clinical studies using intra-articular injections of MSCs have shown significant improvements in pain scores (VAS and AOFAS) and increased range of motion in patients with ankle OA. At a mean follow up of 14.3 months, the mean American Orthopaedic Foot & Ankle Society (AOFAS) score for pain significantly increased from 48.8 preoperatively to 61.1 (P =0.029) and significantly increased from 20.1 preoperatively to 30.1 (P =0.048). The mean VAS score significantly improved from 6.1 to 3.8 at the final follow up (p =0.003) [10]. Thus, the small clinical trial performed by [11] noted significant improvements in both AOFAS and VAS scores at short- to mid-term follow-up. Although this study was performed in patients with advanced stage post-traumatic ankle OA, it gives promise to the benefits that MSCs can provide in earlier stages of ankle OA. Metanalysis of the clinical benefits of MSC injection in knee OA has demonstrated poor study design, high

DOI: https://doi.org/10.52793/JSCR.2026.7(2)-86

risk of bias, and large heterogeneity in current studies [12], and suggests that “more high quality randomized controlled trials with consideration of the potential rehabilitation-driven clinical benefit would be needed”. Further, inconsistencies are noted in the demonstrated benefits of MSC therapy for treatment of chronic knee pain secondary to OA, where [13] reports that “intraarticular injection of MSCs for chronic knee pain associated with knee OA probably provides little to no improvement in pain and functionality”. Thus, additional clinical evidence would be beneficial to confirm the potential benefits of MSC therapy in early-stage OA, particularly for ankle OA where early intervention might provide greater benefit to patients due to its proportionally higher prevalence in younger patients.

The combination of DA with MSC injection is a new treatment option for ankle OA, involving the use of distraction to create a regenerative microenvironment and MSC therapy to further enhance cartilage tissue regeneration, seeking to avoid or delay more invasive joint replacement procedures while preserving ankle motion and function. DA on its own is shown to be a non-effective treatment of ankle OA, where the systematic review [14] outlines that “due to inconsistent improvement in PROMs (patient reported outcome measures), which are likely due to substantial bias, and the high failure rate, this review suggests that distraction arthroplasty is not currently an effective treatment option of ankle arthritis”. Although systematic reviews demonstrate that DA and MSC therapy individually do not lead to consistent therapeutic outcomes for ankle OA, their combination may give rise to synergistic effects and provide a new treatment option, with further research needed to substantiate this hypothesis.

This article reports two cases of ankle OA treated with DA and MSC therapy, with arthroscopic biopsies performed at 12 months to assess cartilage regeneration. The cases highlight distinct histological outcomes, including fibrocartilaginous repair with chondrocytes and hyaline-like cartilage regeneration. The cases offer insights into the regenerative potential of this combined approach and the possible identification of a new repair tissue type.

Case Reports

Case 1: Fibrocartilage with chondrocytes

A 60-year-old male presented with advanced ankle OA, classified as Kellgren-Lawrence grade 3, confirmed through comprehensive diagnostic imaging. Radiographic evaluation revealed significant joint space narrowing, prominent osteophyte formation, and subchondral sclerosis, indicative of advanced degenerative changes. Magnetic resonance imaging (MRI) further confirmed extensive cartilage loss, subchondral bone marrow edema, and synovial inflammation, consistent with severe OA. The patient reported persistent pain, rated 8/10 on the VAS during physical activity, localized primarily to the lateral ankle and Achilles tendon for 4–5 months, with recent onset of discomfort in the left great toe. No joint instability was noted; however, the patient experienced significant functional limitations, particularly difficulty navigating inclines and performing weight-bearing activities. Clinical examination demonstrated restricted ankle range of motion (ROM), with dorsiflexion limited to 10° and plantarflexion to 20°, reflecting significant joint stiffness. The patient, previously an active individual with a history of recreational sports, reported a marked decline in quality of life, including reduced participation in social and physical activities. Following consultation with a general practitioner, the patient was referred for specialist evaluation and subsequently treated at Dr. Gordon Slater’s clinic in 2024.

DOI: https://doi.org/10.52793/JSCR.2026.7(2)-86

1. **Treatment protocol:** Treatment Protocol: The patient underwent DA using a circular Ilizarov external fixator applied to the ankle for 8 weeks to offload mechanical stress and promote a regenerative microenvironment. The fixator was meticulously adjusted to achieve graduated joint space distraction, with radiographic verification performed biweekly to ensure optimal joint spacing (approximately 5 mm). Concurrently, 10 mL of autologous adipose tissue, containing approximately 500,000 cells/mL MSCs, was administered by intra-articular injection under fluoroscopic guidance to enhance cartilage repair [15,16]. Autologous adipose tissue was harvested from the patient's sub-umbilical region using BPB Medica's Lipo-Stem kit. The procedure involved lipoaspiration under local tumescent anesthesia, collecting 60 mL of adipose tissue via a small cannula. The harvested fat was processed in the LIPO-STEM DUO device through micro-fragmentation, continuous saline washing, and dual filtration, yielding purified micro fragmented adipose tissue (MFAT). This MFAT retained MSCs, extracellular matrix (ECM), and growth factors, with the resulting human adipose-derived stem cells (hADPSCs) expressing MSC surface markers and meeting International Society for Cellular Therapy (ISCT) criteria. Notably, these hADPSCs exhibited enhanced regenerative potential including towards a neural lineage, previously demonstrated by elevated expression of neural markers and the formation of neurospheres [15]. The MFAT was injected immediately post-processing to ensure cell viability, avoiding storage or preservation. The postoperative protocol included a touch-weight-bearing regimen for 6 weeks, followed by partial weight-bearing for an additional 6 weeks, supported by a structured physical therapy program to maintain joint mobility and promote muscle strength. Physical therapy emphasized low-impact exercises, including passive ROM and isometric strengthening, to support recovery without compromising the distracted joint.
2. **Clinical Outcomes:** At 3 months post-treatment, the patient reported a significant reduction in pain (VAS: 2/10), reflecting improved joint comfort during daily activities. Ankle ROM improved modestly, with dorsiflexion remaining at 10° and plantarflexion increasing to 30°, indicating partial restoration of joint function. The AOFAS score improved substantially from 52 to 78, signifying enhanced functional capacity and reduced disability. The patient was able to resume low-impact activities, such as walking and cycling, with improved endurance and reduced discomfort, marking a notable improvement in quality of life. Follow-up assessments at 6 and 12 months confirmed sustained pain relief and functional gain, with no reported complications related to the fixator or injection site. Radiographic assessment demonstrated improved ankle joint spacing and alignment following treatment, as demonstrated on lateral and anteroposterior radiographs (Figures 5 and 6).
3. **Histological Findings:** Histological analysis, based on hematoxylin and eosin (H&E) staining of tissue samples obtained during follow-up evaluation at 12 months, revealed fibrocartilaginous repair tissue characterized by embedded chondrocytes and fibroblasts (Figures 1-2). Tissue samples were obtained from the cartilage surface of the ankle joint during removal of distraction screws, with minimal exposure to bare bone. No procedural complications or additional patient harm occurred during sample collection. Higher magnification images demonstrated a dense collagenous matrix with mixed cellular morphology suggestive of fibrocartilaginous repair tissue (Figures 3-4). H&E staining images demonstrated a dense collagen matrix with a fibrous structure, consistent with a fibrocartilaginous phenotype, providing sufficient mechanical stability to support functional improvements but distinct from the ECM organization and composition of native hyaline cartilage. The presence of chondrocytes within this matrix suggests a reparative process, potentially representing an early

or transitional stage of cartilage repair driven by MSC paracrine signalling and the mechanically optimized joint environment created by distraction. Chondrocyte migration, typically occurring at a rate of 1 µm/h, may be influenced by ECM composition or growth factors, potentially enhancing repair dynamics in this context [17]. The biomechanical properties of fibrocartilaginous repair tissue, characterized by a fibrous collagen network, might have contributed to the observed clinical improvements, highlighting the therapeutic potential of the combined approach of DA and MSC therapy in advanced OA.

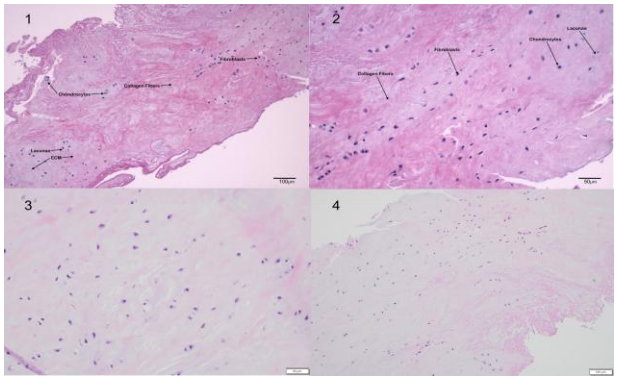

Figure 1, 2, 3, 4: Histological images of H&E staining of retrieved repair tissue at 12 months post-operation, showing the presence of a dense collagen matrix, collagen fibres predominantly type I, chondrocytes, and fibroblasts.

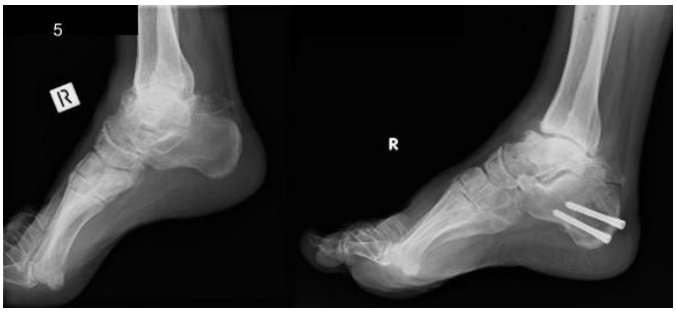

Figure 5: Before and after of right ankle LAT.

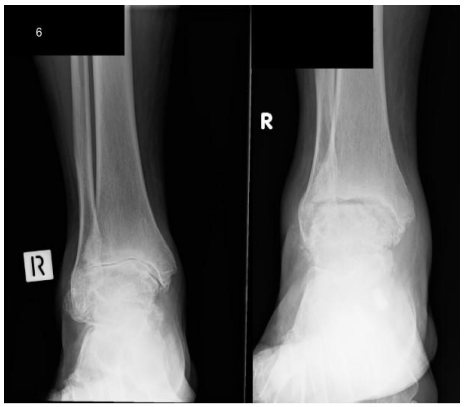

Figure 6: Before and after of right ankle AP.

DOI: https://doi.org/10.52793/JSCR.2026.7(2)-86

Case 2: Hyaline-like cartilage regeneration

A 23-year-old male presented with hemophilic ankle osteoarthritis (OA), diagnosed as Kellgren-Lawrence grade 2, secondary to recurrent hemarthrosis associated with hemophilia. Radiographic imaging revealed moderate joint space narrowing, subchondral sclerosis, and minimal osteophyte formation, with MRI confirming cartilage thinning, focal chondral defects, and no significant bone marrow edema. The patient reported chronic pain (VAS: 6/10), joint stiffness, and impaired ambulation, which significantly restricted an active lifestyle, including participation in recreational sports such as running and soccer. The early onset of OA, driven by repeated intra-articular bleeding, necessitated a regenerative treatment approach to preserve joint function and prevent progression to end-stage disease. Clinical examination revealed reduced ankle ROM, with dorsiflexion of 12° and plantarflexion of 25°, accompanied by mild synovial thickening. The patient's young age, active lifestyle, and desire to avoid invasive interventional procedures prompted the selection of a joint-preserving strategy to restore function and quality of life.

1. **Treatment Protocol:** The patient underwent DA with a circular external fixator applied for 8 weeks, maintaining a consistent 5 mm joint space distraction to reduce mechanical stress and enhance synovial fluid dynamics, creating an optimal environment for cartilage regeneration. Autologous adipose tissue-derived MSCs, processed using the same procedure as in (Case 1) with approximately 500,000 cells/mL [15,16], were administered by intra-articular injection at the time of fixator application under fluoroscopic guidance. The adipose tissue was harvested and processed using the BPB Medica Lipo-Stem kit and LIPO-STEM DUO device, as described in (Case 1), ensuring consistency in MSC quality and delivery. The resulting MFAT, rich in hADPSCs with enhanced regenerative potential, was injected immediately post-processing to maximize cell viability. The postoperative regimen consisted of 6 weeks of non-weight-bearing to protect the distracted joint, followed by progressive weight-bearing over an additional 6 weeks. Physical therapy was tailored to restore proprioception, muscle strength, and joint stability, incorporating aquatic therapy, balance training, and gradual resistance exercises to support functional recovery and prevent reinjury.
2. **Clinical Outcomes:** At 12 months post-treatment, the patient reported minimal pain (VAS: 1/10) and near-normal ankle ROM, with dorsiflexion improved to 15° and plantarflexion to 35°, indicating significant restoration of joint function. The AOFAS score increased from 58 to 85, reflecting substantial functional recovery and improved quality of life. Follow-up MRI demonstrated restored joint space, homogeneous cartilage signal intensity, and resolution of focal chondral defects, with no evidence of bone marrow edema, suggestive of cartilage tissue restoration. The patient resumed moderate physical activities, including jogging and recreational sports, without recurrence of hemarthrosis or joint instability, demonstrating a robust clinical outcome. Follow-up assessments at 6 and 12 months confirmed sustained functional improvements, with no complications related to the fixator or injection site. The patient's ability to return to an active lifestyle highlighted the efficacy of the combined therapy in a younger patient with early-stage OA and a favorable joint microenvironment.
3. **Histological Findings:** Histological analysis, based on H&E staining of tissue samples obtained during follow-up evaluation at 8 weeks, revealed hyaline-like cartilage regeneration, a significant finding in ankle OA (Figures 7A-D). H&E staining images demonstrated a smooth articular surface

DOI: https://doi.org/10.52793/JSCR.2026.7(2)-86

with a well-organized matrix and chondrocytes arranged in lacunae, suggestive of the morphology of hyaline-like cartilage. The tissue exhibited structural characteristics distinct from fibrocartilage, with a homogeneous matrix and minimal fibrous components, as well as organized chondrocyte distribution, indicating a repair tissue resembling some of the characteristics of hyaline cartilage. These findings underscore the potential of combined DA and MSC therapy to achieve an optimized joint microenvironment enabling high-quality cartilage regeneration in a younger patient with early-stage disease.

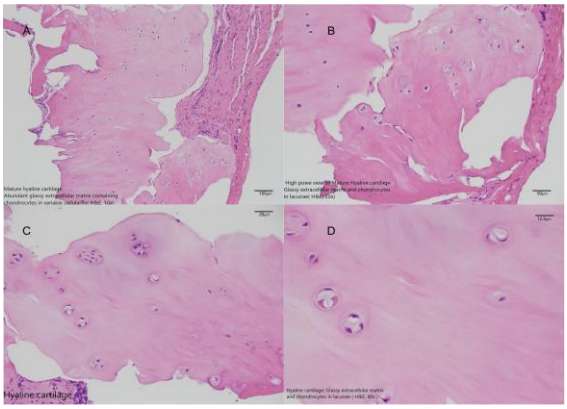

Figure 7: H&E staining showing development of hyaline cartilage. A) 10X view displaying mature hyaline cartilage, abundant glassy extracellular matrix containing chondrocytes. B) 20X view displaying clear chondrocytes and hyaline cartilage. C) 30X view displaying hyaline cartilage. D) 40X view showing chondrocytes in lacunae.

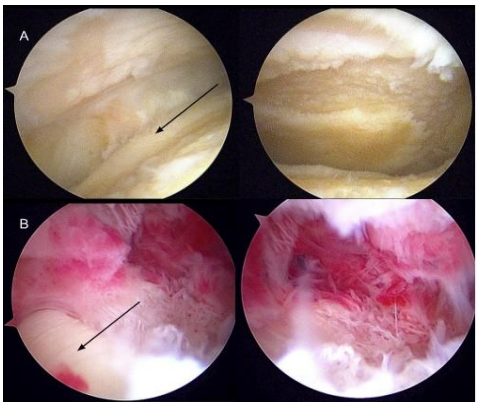

Figure 8: Arthroscopic images of the medial talar dome before and after treatment. (A) Pre-treatment arthroscopic image demonstrating advanced osteoarthritic degeneration with exposed subchondral bone at the talar dome (arrow). (B) Follow-up arthroscopic image demonstrating surface tissue infill at the previously denuded region adjacent to native cartilage (arrow), suggestive of reparative cartilage formation.

Discussion

Possible mechanisms of action

DA promotes cartilage repair by reducing mechanical stress on the joint [18], improving synovial fluid dynamics, and creating a low-inflammatory microenvironment conducive to regeneration [19]. The external fixator maintains joint space, preventing cartilage compression and facilitating nutrient diffusion.

DOI: https://doi.org/10.52793/JSCR.2026.7(2)-86

The intra-articular delivery of MSCs provides paracrine action at the site of cartilage damage. Preclinical studies suggest that MSCs act through inflammatory modulation and paracrine signalling to promote joint repair, enhancing cartilage and other tissue regeneration through the secretion of bioactive molecules such as extracellular vesicles, cytokines, and growth factors, delivering therapeutic effects including promote anti-inflammatory signalling, chondroprotection, matrix synthesis, and mitochondrial transfer [20,21,22,23]. For example, some of the biomolecules key to MSC paracrine signalling include TNF-stimulated gene 6 (TSG-6) that decreases synovitis and protects cartilage, Prostaglandin E2 (PGE2) that reduces joint inflammation [24,25], transforming growth factor β (TGF-β) that enhances cartilage matrix production [26], and insulin-like growth Factor 1 (IGF-1) that stimulates resident chondroprogenitor cells and modulates inflammation [27]. The combination of mechanical unloading and regenerative cell therapy likely synergizes to optimize cartilage repair outcomes.

Histological variability

The distinct histological findings in these two cases provide insights into the spectrum of possible cartilage repair outcomes. In (Case 1), the presence of fibrocartilage with embedded chondrocytes suggests a reparative process that, while not forming hyaline-like cartilage, produces a mechanically functional tissue. Fibrocartilage, rich in type I collagen, is less durable than hyaline cartilage, but may provide superior tensile strength in the short-term [28], thus aiding joint stability and pain relief, evidenced by the patient's improved AOFAS score and reduced VAS.

The divergent histological outcomes of fibrocartilage in case 1 compared to hyaline-like cartilage in case 2 likely reflect differences in the intrinsic regenerative potential and joint microenvironment in individuals rather than direct MSC differentiation. While the injected MSCs are not likely to persist long-term within the joint [29], their paracrine signaling may activate resident repair cells such as chondroprogenitors [30,31,32]. The superior hyaline-like tissue regeneration in the 23-year-old patient aligns with evidence that younger MSCs exhibit greater trophic factor secretion and responsiveness to mechanical stimuli, while the 60-year-old patient's fibrocartilaginous repair reflects age related MSC senescence and a degenerative joint environment [33]. Moreover, the K-L 2 grade OA joint in Case 2, being at an earlier disease stage, might have retained more favorable conditions for regeneration, with the DA procedure providing critical mechanical unloading that enhanced nutrient diffusion and endogenous repair processes. Although fibrocartilage lacks the biochemical characteristics of native hyaline cartilage, its formation in (Case 1) provided functional improvement, demonstrating that even in advanced OA the combined approach of DA and MSC therapy can yield clinically meaningful outcomes. These cases underscore that patient age, disease stage, and mechanical environment all determine therapeutic success, with other factors such as MSC quality and host response also contributing to differences in clinical outcomes, further suggesting that younger patients with early OA may gain more benefit from this dual treatment strategy.

Clinical implications

Both patients experienced significant clinical improvements, underscoring the therapeutic potential of coupling DA with MSC therapy. The restoration of joint space, pain reduction, and functional improvement suggest that this combinational approach may delay or even eliminate the need for joint arthroplasty,

particularly in younger patients. The histological findings, particularly the hyaline-like cartilage regeneration in (Case 2), highlight the potential for biologically superior outcomes, which could contribute to redefining treatment paradigms for ankle OA.

The fibrocartilaginous-chondrocyte tissue observed in Case 1 may represent a novel repair phenotype with unique biomechanical properties. Further characterization of this tissue, through advanced imaging and detailed molecular analyses, could elucidate its role in cartilage repair and its potential for progression to hyaline-like cartilage repair. These findings support the need for larger, controlled trials to optimize treatment protocols, including MSC dosing, distraction duration, and patient selection criteria.

Compared to conventional intra-articular MSC injection, combination with DA could enhance MSC survival through biological mechanisms such as reduction of apoptotic stress, enhancement of nutrient diffusion, synovial microenvironment modulation, and Mechan transduction effects. In particular, DA could help alleviate shear stress normally experienced by MSCs during conventional intra-articular injection due to syringe passage and inflammatory joint fluid, which can trigger apoptosis [34]. Moreover, mechanical offloading in DA may reduce pro-inflammatory cytokines and oxidative stress, facilitate a more pro-regenerative environment [35] as well as increase synovial fluid flow and reduce intra-articular pressure [36], hence potentially improving oxygen and nutrient diffusion to MSCs. Further, DA can help reduce synovitis and fibrosis [37] by decreasing MMP-13 and increasing hyaluronic acid secretion, as well as play a mechanotransducive role by providing cyclic tensile strain, which can in turn activate YAP/TAZ signaling in MSCs, promoting survival and antiapoptotic gene expression [38]. Thus, controlled joint DA combined with MSC therapy may provide a range of synergistic therapeutic effects in alleviating the symptoms and progression of OA. Future studies tracking labeled MSCs in distracted joints are needed to confirm the aforementioned mechanistic hypotheses.

Limitations and future directions

The small sample size in these two case studies limits generalizability, and the variability in histological outcomes underscores the need to identify predictors of hyaline and fibrocartilaginous tissue repair. Future studies should investigate the role of patient-specific factors (e.g., age, OA etiology, joint microenvironment), MSC characteristics (e.g., source, culture conditions), adjunctive therapies (e.g., growth factors, biomaterial scaffolds), and molecular biomarkers associated with cartilage regeneration and inflammation, including chondrogenic markers such as SOX0, aggrecan and collagen type II. Long-term follow-up is essential to assess the durability of repaired cartilage and its impact on joint function.

Conclusion

This report demonstrates the efficacy of DA combined with MSC therapy in treating ankle OA, with patients in both cases achieving significant clinical improvements. The histological outcomes provide novel insights into cartilage repair mechanisms. Case 2 represents the first documented instance of hyaline-like cartilage regeneration in the ankle using this combined approach, a landmark achievement in regenerative orthopaedic. The fibrocartilaginous tissue with embedded chondrocytes observed in (Case 1) may represent a new tissue type, potentially serving as a functional intermediate in the cartilage repair process. These findings highlight the transformative potential of combining DA with MSC therapy in treating OA of

DOI: https://doi.org/10.52793/JSCR.2026.7(2)-86

the ankle and potentially other joints, underscoring the need for further research to refine and standardize this promising treatment modality.

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